REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 37, 45-48, 50-59, 62, 63, 69, 72, 74, 78 and 79 have been amended herein such that each independent claim recites two or four different oligonucleotide sequences, with each oligonucleotide having a length limitation. As a results of these amendments, claims 38-44, 64-68 and 75-77 have been canceled without prejudice to continued prosecution.

Claims 37, 45-63, 69-74, 78 and 79 are currently pending. Reconsideration of the pending application is respectfully requested.

The 35 U.S.C. §112 Rejection

Claim 45 stands rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserted that the recitation of '50' cycling steps is new matter since the original claims recited '45' cycling steps.

Without acquiescing to the Examiner's rejection, Applicants have amended claim 45 to recite '45' instead of '50' cycling steps. In view of this amendment, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §103 Rejections

Claims 37-79 stand rejected as being obvious over a number of different references in various combinations. Basically, the Examiner is using Buck et al., which teaches that numerous sequencing primers all functioned in a sequencing reaction, to support an argument that any real-time PCR primer or probe is obvious in view of the disclosure of the *pts* gene sequence (the Telford reference) and the disclosure of using PCR amplification to detect GBS (the Bergeron reference) or another microorganisms (the Bellin and Uhl references). The remaining references cited by the Examiner are directed toward various aspects of PCR amplification (Wittwer I, Pfeffer, and Tyagi) or other dependent claims directed toward, for example, preventing contamination (Hartley, Wittwer II, and Livak). The issue here is the obviousness of the specifically-recited oligonucleotides (e.g., the *pts* primers and the *pts* probes). According to the

Examiner, the "prior art provides ample guidance to construct primers and probes from known sequences for use in the claimed methods, including the sequence from which to construct the primers and probes."

Without acquiescing to the Examiner's rejections, independent claims 37 and 63 have been amended to recite four different oligonucleotide sequences and independent claim 74 has been amended to recite two different oligonucleotide sequences. Each oligonucleotide recited in the claims includes a limitation that the oligonucleotides are no more than 30 nucleotides in length. The particularly claimed combination of two or four different oligonucleotides is not obvious over the general disclosure of a gene or a genomic sequence, even in view of Buck et al. (or Lowe et al., cited in the IDS attached hereto) for the reasons discussed below.

The Examiner is using Buck et al. as a reference that ostensibly provides both motivation and a reasonable expectation of success (i.e., that any oligonucleotide will work). Buck et al. is not relevant to the obviousness of the claimed methods, however, for a number of reasons. First, Buck et al. did not use *pts* nucleic acid sequences nor did Buck et al. use GBS nucleic acid sequences. Also, even ignoring the fact that Buck et al. did not use GBS nucleic acids, an automated sequencing reaction as described in Buck et al. is significantly different than a PCR amplification reaction in which, generally, at least two oligonucleotides are used, or a real-time PCR amplification reaction in which, generally, three or four oligonucleotides are used. Using a single oligonucleotide in a sequencing reaction as Buck et al. does is vastly different than using two, three, or four oligonucleotides in a real-time PCR amplification reaction. The premise of Buck et al. *may* be true for sequencing reactions on the template DNAs reported therein, but it is certainly not true for amplification reactions, particularly real-time amplification reactions, on completely different template nucleic acids.

In addition, the results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions. Primer design for PCR amplification and primer and probe design for real-time PCR amplification and frequently is not predictable. Applicants respectfully refer the Examiner to the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility, which states "...be aware that no set of guidelines will always

accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."

In addition, there are several peer-reviewed publications (copies of which are attached herein with the enclosed Information Disclosure Statement) that compare different primer sets or compare the same primer set under different amplification conditions. For example, Csordas et al. (2004, *Lett. App. Microbiol.*, 39:187-193) state that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR" (see the Abstract); Elnifro et al. (2000, *Clin. Microbiol. Rev.*, 13:559-570) state that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (first full sentence on page 560); Tichopad et al. (2004, *Mol. Cell. Probes*, 18:45-50) state that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see the Abstract); and Abd-Elsalam (2003, *African J. Biotech.*, 2:91-95) states that "...the most critical parameter for successful PCR is the design of primers" (see first full paragraph on page 94). See also Ballard et al., 2005, *Antimicrob. Agents Chemotherapy*, 49:77-81. These references clearly demonstrate the unpredictability of primer and probe design.

Applicants are aware of no case law standing for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. In fact, based on the current case law, each of the claimed primer and probe sequences are not obvious over the cited references, and certainly not the particularly recited combination of two or four sequences. See, for example, *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) ("[t]hat the claimed compound is a species of a genus disclosed in a prior art reference does not necessarily make the compound prima facie obvious") and *In re Bell*, 991, F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) ("given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious"). See, also, *In re Deuel* (51 F.3d 1552, 34 UPSQ2d 1210 (Fed. Cir. 1995)), which also stands for the non-obviousness of a sequence. Specifically, *In re Deuel* states that methods of isolating and making specific DNA molecules are

not obvious over prior art that does not disclose the specific DNA molecules. The lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

There are a number of decisions including those discussed herein indicating that a species (in this case, a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length sequence disclosed in the prior art to which the oligonucleotide has complementarity). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an 'invention of selection') is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen v. Chugai*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) ["a gene is a chemical compound"].

The current rejections of method claims that use specific primer or probe sequences are not consistent with the standard for obviousness and with the current case law regarding obviousness. According to a recent Supreme Court decision (*KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ____ (2007)), "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)). Applicants believe the Examiner is making conclusory statements regarding the efficacy of 'all primers' based on Buck et al. when, in fact, Applicants have provided evidence in the form of more-recently published references that discuss and provide experimental evidence demonstrating the unpredictability of primer and probe design. According to the Supreme Court, "[t]he fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that [the claim] was not obvious to those skilled in the art."

In view of the amendments and remarks herein, Applicants respectfully request that the rejections of the pending claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully request allowance of claims 37, 45-63, 69-74, 78 and 79. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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